

THYROID STATUS IN TROPHOBLASTIC DISEASES

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SUMMARY

Twenty cases of gestational trophoblastic disease were compared with euthyroid pregnant and non-pregnant controls as regards clinical, biochemical and radio-immunological evidences of thyroid hyperfunction and analysed statistically with respect to pre and post treatment status and gravindex slide test results.

Clinically as well as biochemically 6 molar pregnancy and 2 choriocarcinoma cases were moderately hyperthyroid, 4 molar pregnancy and 1 choriocarcinoma cases were mildly hyperthyroid. The rest were euthyroid. The usual discrepancy found between clinical and biochemical thyroid status was not seen in the present series.

The judicious management on the whole may not include sophisticated investigations for thyroid status nor is a specific treatment required for controlling hyperthyroidism in these cases.

Introduction

In the complex and multifarious endocrine adjustment that takes place during a normal pregnancy there has been a well documented clinical, histological, biochemical, biophysical and immunochemical evidence of physiologic hyperactivity of the thyroid gland. However, in molar pregnancy as well as other trophoblastic disease there is a real enhancement of thyroid function.

In the majority of studies the clinical manifestation of thyrotoxicosis in trophoblastic diseases falls short of the laboratory evidence of increased thyroid function.

This work was taken up (a) to study the thyroid status in trophoblastic diseases in this part of the country (b)

to find out the relationship of hyperthyroidism with unexplained catastrophic manifestations in molar-pregnancy cases in our hospitals and (c) to find out how study of thyroid function would affect management of such cases.

Material and Methods

Sixteen cases of molar pregnancy between the ages 18 and 40 and 4 cases of choriocarcinoma between the ages 25 and 42 years were studied and compared with 5 pregnant and 5 non-pregnant controls of matching ages.

The thyroid status of the cases was grouped clinically as euthyroid, mildly hyperthyroid or moderately hyperthyroid, based on the following features, namely nervousness, increased sweating, hypersensitivity to heat, palpitation, fatigue, weightloss, tachycardia, dyspnoea, weakness, increased appetite,

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goitre, tremor, bruit over the thyroid, exophthalmus and exaggerated tendon reflexes.

Gravindex kit using the principle of agglutination of adsorbed latex particle.

Biochemical Tests

Ten millilitre blood was drawn from antecubital vein. The serum was separated and sealed and stored in deep freeze and subjected to the following tests as and when the kits arrived.

(1) Serum protein bound Iodine (P.B.I.) was estimated by Alkaline Ash method of Barker and Humphrey (1950).

(2) Serum total triiodothyronin (T3) by radio immunoassay (RIA) using the T3 RIA kit of Bhabha Atomic Research Centre (B.A.R.C.), Trombay.

(3) Serum total thyroxine (T4) using the T4 RIA kit of B.A.R.C.

(4) 2 hours and 24 hours radio Iodine uptake (^{131}I) at the Isotope laboratory of the cancer institute attached to S.C.B. Medical College.

(5) Immunological slide test of human chorionic gonadotropin (Hcg) by the

Observations

The frequency of symptoms associated with hyperthyroidism in all the 20 cases were studied.

Classification into moderate and mild hyperthyroidism clinically was done by presence of tremor and hyperactive reflexes and hyperactive reflex alone respectively. The rest were euthyroid.

Tables I and II shows the incidence of clinical hyperthyroidism before and after treatment. Of the 16 molar pregnancy cases, 6 were moderately hyperthyroid, 4 were mildly hyperthyroid and 6 were euthyroid before evacuation of the moles. Two out of 4 choriocarcinoma cases were moderately hyperthyroid, 1 was mildly hyperthyroid and 1 euthyroid before chemotherapy. After 8th day of evacuation of moles, 11 out of the 12 cases followed were euthyroid. One case still showed mild hyperthyroid features. One out of the 4 choriocarcinoma cases still showed mild hyperthyroidism after 2 courses of methotrexate.

TABLE I
Incidence of Clinical Hyperthyroidism Before Treatment

Type of cases	Total No.	Euthyroid		Mildly hyperthyroid		Moderately hyperthyroid	
		No.	%	No.	%	No.	%
Molar pregnancy (before evacuation)	16	6	37.5	4	25	6	37.5
Choriocarcinoma (before treatment)	4	1	25	1	25	2	50
Total cases studied	20	7	35	5	25	8	40

TABLE II
Incidence of Clinical Hyperthyroidism After Treatment

Type of cases	Total No.	Euthyroid		Mildly hyperthyroid	
		No.	%	No.	%
Molar pregnancy (after treatment) (8-12 days)	12	11	91.7	1	8.3
Choriocarcinoma (7 days after treatment)	4	3	76	1	25.0
Total cases after treatment	16	14	87.5	2	12.5

Table III shows the mean values \pm standard deviation of T_3 , T_4 and P.B.I. in molar pregnancy cases prior to and after evacuation side by side with pregnant and non-pregnant controls. Pre-evacuation T_4 (Serum total thyroxine) varied from 4.8 $\mu\text{g}/100$ ml to 30 $\mu\text{g}/100$ ml with a mean of 14.65 ± 9.80 $\mu\text{g}/100$ ml. Post evacuation levels ranged between 3.9 $\mu\text{g}/100$ ml to 15.3 $\mu\text{g}/100$ ml with a mean of 7.52 ± 3.38 $\mu\text{g}/100$ ml. The mean T_4 level of pregnant and non-pregnant controls, were $7.3 \pm \text{S.D. } 0.88$ $\mu\text{g}/100$ ml and $5.68 \pm \text{S.D. } 1.82$ $\mu\text{g}/100$ ml respectively. Pre-evacuation T_3 (Serum total triiodothyronin) ranged from 0.3 nanogram/ml. (a hypothyroid value) to 5.3 nanogram/ml. The mean being $2.53 \text{ S.D. } \pm 1.83$ nanogram/ml. Post evacuation levels varied between 0.1 nanogram/ml to 3.0 nanogram/ml with a mean of

1.58 S.D. ± 0.93 nanogram/ml. The mean T_3 level of non-pregnant controls was $1.64 \text{ S.D. } \pm 0.26$ nanogram/ml and that for pregnant controls was 2.1 ± 0.41 nanogram/ml.

Pre and post evacuation serum protein bound Iodine (P.B.I.) levels ranged between 4 microgram/100 ml and 12 microgram (μgm)/100 ml and 3 $\mu\text{gm}/100$ ml to 7 $\mu\text{gm}/100$ ml respectively with mean values of $7.68 \text{ S.D. } \pm 2.98$ and $4.66 \text{ S.D. } \pm 1.33$ $\mu\text{gm}/100$ ml. These varied significantly from each other, ($P < 0.05$). The mean levels in non-pregnant and pregnant controls were $4.0 \text{ S.D. } \pm 0.63$ $\mu\text{gm}/100$ ml and $6.0 \text{ S.D. } \pm 1.09$ $\mu\text{gm}/100$ ml respectively.

Table IV shows the biochemical parameters with respect to clinical thyroid status in molar pregnancy cases prior to

TABLE III
Mean \pm S.D. of T_3 , T_4 and P.B.I. in Molar Pregnancy Cases Before and After Treatment Compared to Controls

Type of case	T_3 in ng/ml (Mean \pm S.D.)	T_4 in Ugm/ml (Mean \pm S.D.)	PBI in Ugm/ml (Mean \pm S.D.)
Molar pregnancy:			
Before treatment	2.53 ± 1.83	14.65 ± 9.80	7.68 ± 2.98
After treatment	1.58 ± 0.93	7.52 ± 3.38	4.66 ± 1.33
Normal pregnant controls	2.1 ± 0.41	7.30 ± 0.88	6.00 ± 1.09
Non-Pregnant controls	1.69 ± 0.26	5.68 ± 1.82	4.00 ± 0.63

TABLE IV
Biochemical Parameters With Respect to Clinical Thyroid Status in Molar Pregnancy (Prior to evacuation)

Clinical status	No. of Obs.	T ₃ ng/ml	T ₃ /T ₄	No. of Obs.	T ₄ µg/100 ml	PBI µg/100 ml
(a) Euthyroid	6	0.98 ± 0.50	0.0138 ± 0.007	6	7.35 ± 2.34	4.83 ± 1.6
Variation of (a) with (b)		P < 0.05	P < 0.05		P < 0.05	P < 0.05
(b) Mildly hyperthyroid	2	2.75 ± 0.07	0.0197 ± 0.0176	4	19.15 ± 8.33	8.4 ± 2.5
Variation of (b) with (c)		P < 0.05	P < 0.05		P < 0.05	P < 0.05
(c) Moderately hyperthyroid	4	4.73 ± 0.78	0.0334 ± 0.0095	6	18.92 ± 8.33	10 ± 1.9
Variation of (a) with (c)		P < 0.05	P < 0.05		P < 0.05	P < 0.05

evacuation with the T₃/T₄ ratios and their P-values prior to evacuation. There is significant statistical variation between T₃ values when they are grouped into their clinical status. Each of the sub-group varied significantly from euthyroid, non-pregnant and pregnant controls (P < 0.01 to < 0.05).

The mean T₃ values in the euthyroid, mildly hyperthyroid and moderately hyperthyroid were 0.98 S.D. ± 0.50 ng/ml, 2.75 S.D. ± 0.07 ng/ml and 4.73 S.D. ± 0.78 ng/ml. Mean T₄ values in the same order were 7.35 S.D. ± 2.34 µgm/100 ml, 19.15 S.D. ± 8.33 µgm/100 ml and 18.92 S.D. ± 8.33 µgm/100 ml respectively. T₃/T₄ ratios were 0.0138 S.D. ± 0.007, 0.0197 S.D. ± 0.0176 and 0.033 S.D. ± 0.0095 respectively all with significant P values

Serum P.B.I. levels in the three groups in the same order were 4.83 S.D. ± 1.6 µgm/100 ml, 8.4 S.D. ± 2.5 µgm/100 ml and 10 S.D. ± 1.9 µgm/100 ml respectively. All showed highly significant P values in their variation.

Table V shows the biochemical profile in the choriocarcinoma cases before and after treatment. Only 4 cases were studied of which 3 were given chemotherapy and one under-went total abdominal hysterectomy with bilateral salpingo-oophorectomy. Mean pre-treatment values of T₃, T₄, and P.B.I. were 4.38 S.D. ± 3.4 ng/ml, 18.25 S.D. ± 7.31 µgm/100 ml and 8.75 S.D. ± 2.23 µgm/100 ml respectively.

Post chemotherapy values of T₃, T₄ and P.B.I. were 1.13 S.D. ± 1.04 ng/ml, 7.05 S.D. ± 1.34 µgm/100 ml and 5.67 S.D. ± 0.58 µgm/100 ml; all these were different significantly from the pre treatment values (P < 0.05).

Radio Iodine (131 I) uptake was done in 9 cases, 2 non-pregnant controls and 2 pregnant controls waiting for termination

TABLE V
Biochemical Profile of Choriocarcinoma Cases Before and After Treatment

	T ₃ (ng/ml)	T ₄ Ugm/100 ml	PBI Ugm/100 ml
Pre Treatment (Mean ± S.D.)	4.38 ± 3.4	18.25 ± 7.3	8.75 ± 2.2
Post Treatment (Mean ± S.D.)	1.13 ± 1.0	7.05 ± 1.3	5.67 ± 0.6
Variation	P<0.05	P<0.05	P<0.05

of pregnancy for failed contraception. The control groups showed euthyroid 2 hours and 24 hours uptakes viz. 10.05 S.D. ± 0.07% and 14.55 S.D. ± 1.05% 2 hours uptakes and 23.3 S.D ± 0.98% and 39.65 S.D. ± 7.5% 24 hours uptake respectively in non-pregnant and pregnant controls. The mean 2 hours and 24 hours 131 I uptake in molar pregnancy cases prior to evacuation were 31.55 ± 17.54% and 58.1 ± 28.03. It fell to 7.93 ± 2.0 and 22.55 ± 7.93 after evacuation. Their significance has been illustrated in Table VI.

Table VII shows the correlation between the qualitative test for human chorionic gonadotropin in urine prior to evacuation and the clinical thyroid status in molar pregnancy cases. Distributing the qualitative tests results of Hcg in urine in the neat and dilutions with respect to clinical status a positive relation is observed. 66.67% of euthyroid molar pregnancy cases showed neat positive results. 50% of mildly hyperthyroid showed a positive test in 1:200 dilution and 66.67% of the moderately hyperthyroid group showed a positive test 1:500 dilu-

TABLE VI
Radio Iodine (131 I) Uptake Results in Molar Pregnancy Cases (Pre and Post evacuation) Along With Controls

	Mean ± S.D. 2 hour uptake in % uptake	Mean ± S.D. 24 hour uptake in % uptake	Variation
(a) Molar pregnancy (Pre evacuation)	31.55 ± 17.5	58.1 ± 28.03	a:b P<0.05 a:c P<0.05 a:d P<0.01
(b) Post evacuation	7.93 ± 2.0	22.55 ± 7.9	b:c P<0.05 b:d P<0.05
(c) Pregnancy controls	23.3 ± 1.0	39.65 ± 7.5	c:d P<0.05
(d) Non-pregnancy controls	10.05 ± 0.1	14.55 ± 1.1	

TABLE VII
Correlation Between Qualitative Test for Human Chorionic Gonadotropin and Clinical Thyroid Status in Molar Pregnancy

Gravindex slide test clinical thyroid status (Pre-evacuation)	1:1 —ve (Neat negative)	1:100 —ve (Neat positive)	1:300 —ve (1:200 positive)	1:400 —ve (1:200 positive)	1:500 —ve (1:400 positive)	1:1000 —ve (1:500 positive)	Total
Euthyroid	1 (16.69%)	4 (66.67%)	0	1 (16.67%)	0	0	6
Mildly hyperthyroid	1 (25%)	1 (25%)	2 (50%)	0	0	0	4
Moderately hyperthyroid	0	1 (16.67%)	1 (16.67%)	0	0	4 (66.67%)	6
Total	2	6	3	1	0	4	16

tion of the urine. Conversely no case of moderately hyperthyroid group gave a negative result. Where as none of the clinically euthyroid patients showed a positive result in 1:500 dilution. The number of observations is too few to give a satisfying X^2 test. However, within the limitations the results appear significant.

Discussion

Laboratory evidence of increased thyroid function is characteristic of trophoblastic disease. Increased B.M.R., serum P.B.I. Butanol-extractable Iodine (B.E.I.). 2 hours, 4 hours, 6 hours, 24 hours Radio Iodine uptake, raised serum total triiodothyronin (T_3) and thyroxine (T_4) decreased levels of pituitary thyrotropin (T.S.H.) and serum cholesterol, insensitivity of pituitary to Thyrotropin Releasing Hormone (TRH). Stimulation have all been noted with statistical significance. All parameters return to normal by 7 days after evacuation of the mole (Dowling *et al* 1960, Koch *et al* 1966, Higgins and Hershman *et al* 1975, Nagatani *et al* 1977). Post Chemotherapy thyroid function in choriocarcinoma returns to normal with the success of the treatment. Cohen and Utiger 1970, report a normal serum P.B.I. and thyroxine (T_4) after 3 weeks of chemotherapy with methotrexate and actinomycin.

In the studies made by Hershman and Higgins (1975) 64.28% of the cases of molar pregnancy and choriocarcinoma were clinically hyperthyroid, whereas biochemically 71.4% were hyperthyroid. In the present study, 65% were clinically hyperthyroid and the same 65% had raised hormone levels also. Dowling *et al* (1960) showed a 40% incidence of clinical hyperthyroidism, whereas 100% of their cases were biochemically hyper-

thyroid. Nagataki *et al* (1977) report 70% cases biochemically hyperthyroid with a clinically euthyroid status in all cases. Most other authors viz Koch and Kessel (1966) Odell *et al* (1963) Winand and Bates (1969) Osathanondh *et al* (1978) Miyal *et al* (1976) have reported this kind of discrepancy between clinical status and biochemical profile. Of the several speculations explaining the reason for this discrepancy two are most convincing.

(a) Low Free T₃ (FT₃) concentration is found in trophoblastic diseases which is responsible for a lack of overt manifestation of hyperthyroidism. (Osathanondh *et al* 1976). This has not been estimated in the present series.

(b) Low T₃/T₄ ratio (Nagataki *et al* 1977) is also found in trophoblastic disease. Generally the higher the ratio the more overt is the manifestation of thyrotoxicosis. In the series reported by Hershman and Higgins (1975) where there is no discrepancy the T₃/T₄ ratio corresponds to the clinical status. In their studies T₃/T₄ ratio has been compared with the T₃/T₄ ratio in the present series in the following (Table VIII).

Thyroid storm and cardiovascular complications have been noted by Cohen and Utiger (1970) in one case of choric-

carcinoma. Chemotherapy with methotrexate and actinomycin-D rather than antithyroid drugs and digitalization helped the patient to recover. In severe thyrotoxicosis in 2 cases of molar pregnancy reported by Hershman and Higgins (1970) there was no response to carbimazole. It was only hysterotomy and removal of molar tissue that helped the patient to recover from acute cardiovascular crisis and pulmonary oedema.

Two molar pregnancy cases (prior to this study) in the department of obstetrics and gynaecology, S.C.B. Medical College, Cuttack suddenly developed chest pain and pulmonary oedema and died within minutes before anything could be done. Both had tachycardia and hyper-dynamic circulation but unfortunately their clinical thyroid status had not been evaluated.

The general impression from the results is that a routine clinical assessment and one or two quick feasible investigations like a 2 hours 131 Iodine uptake could be done to know the severity of the thyroid state in clinical situations for early management to prevent a thyroid crisis. Sophisticated investigations for thyroid status are not recommended neither is any specific medical or surgical antithyroid treatment indicated.

TABLE VIII
Comparative Table of T₃/T₄ Ratio

Author	Mean T ₃ /T ₄ + S.D.		
	Moderately hyperthyroid	Mildly hyperthyroid	Euthyroid
Hershman and Higgins (1975)	0.0224 ± 0.0063	0.0178 ± 0.0007	0.0135 ± 0.0529
Present series	0.0334 ± 0.0095	0.0192 ± 0.0176	0.0138 ± 0.0077

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